

# The metabolic profile of TMC278, an investigational NNRTI

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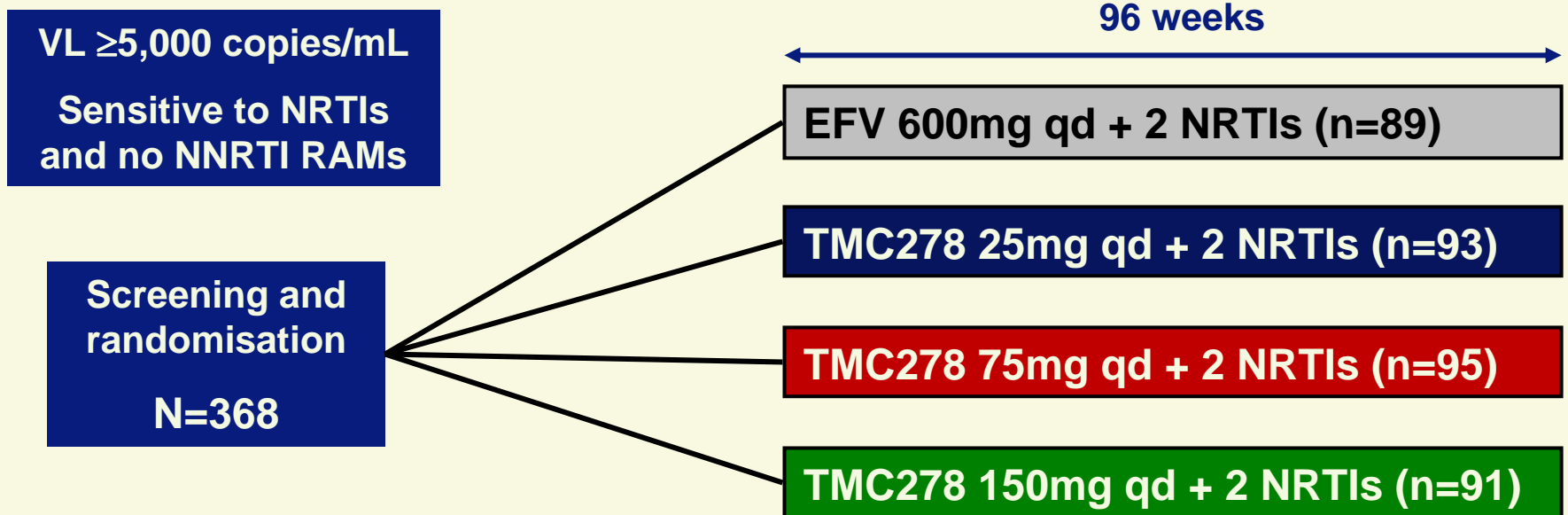
# Background

- **TMC278, a next-generation NNRTI, has demonstrated *in-vitro* activity against wild-type and NNRTI-resistant isolates<sup>1</sup>**
- **48-week results from an ongoing Phase IIb dose-finding study (TMC278-C204) demonstrated the potent and sustained efficacy of TMC278 qd in ARV-naïve, HIV-1-infected patients<sup>2</sup>**
- **Efavirenz (EFV) is commonly associated with metabolic disturbances, particularly increases in cholesterol and triglyceride levels<sup>3</sup>**

<sup>1</sup>de Béthune MP, et al. CROI 2005. Abstract 556; <sup>2</sup>Pozniak A, et al. CROI 2007. Abstract 144LB

<sup>3</sup>Bristol-Myers Squibb Company. Revised FDA label for EFV. February 2005

# 48-week primary analysis of TMC278-C204, a Phase IIb study in ARV-naïve HIV-1-infected patients



- Ongoing, randomised, active controlled, dose-finding study
- TMC278 blinded for all three dose groups *versus* open-label EFV
- Stratification factors
  - investigator-selected NRTI backbone: AZT/3TC (75.3%) or TDF/FTC (24.7%) (given as combination or individual components)
  - region (Asia and Africa; USA, Europe and Russia; Latin America)

VL = viral load; RAM = resistance-associated mutation

# Objectives and methods

- **To assess the metabolic profile of TMC278 in comparison with EFV in trial TMC278-C204**
- **Measured changes from baseline in**
  - **total cholesterol (TC)**
  - **low-density lipoprotein-cholesterol (LDL-C)**
  - **high-density lipoprotein-cholesterol (HDL-C)**
  - **triglycerides (TG)**
  - **glucose**
- **Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated**
- **Samples were taken at screening, baseline, and Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48**

# Demographic and baseline characteristics

Characteristic	Combined TMC278 group (n=279)	EFV 600mg group (n=89)
Female, (%)	33.0	32.6
Caucasian, (%)	44	47
Age, years	35	35
VL, copies/mL*	69,300 (144–13,600,000)	75,100 (2,320–2,570,000)
VL, log <sub>10</sub> copies/mL*	4.84 (2.16–7.13)	4.88 (3.37–6.41)
CD4 count, cells/mm <sup>3†</sup>	200 (5–758)	207 (3–970)
Duration of known HIV infection, years*	1.0 (0–21)	1.0 (0–15)

\*Median values and (range); †n=88 for EFV

# Baseline metabolic parameters

Parameter†	TMC278			Combined TMC278 group	EFV 600mg group
	25mg	75mg	150mg		
TC (mg/dL)	157 (33)	159 (37)	162 (36)	159 (35)	157 (35)
LDL-C (mg/dL)	92 (28)	91 (33)	95 (32)	93 (31)	95 (30)
HDL-C (mg/dL)	39 (13)	40 (12)	42 (13)	40 (13)	39 (11)
Ratio TC/HDL-C	4.4 (1.5)	4.3 (1.5)	4.1 (1.3)	4.3 (1.3)	4.2 (1.0)
TG (mg/dL)	134 (74)	143 (102)	127 (81)	135 (87)	117 (59)
Glucose (mg/dL)	89 (12)	89 (13)	91 (19)	90 (15)	93 (26)
Log (HOMA-IR)	2.2 (0.7)	2.2 (0.8)	2.2 (0.7)	2.2 (0.7)	2.3 (0.8)

\*†Mean (standard deviation)

# Mean changes from baseline in metabolic parameters at 48 weeks

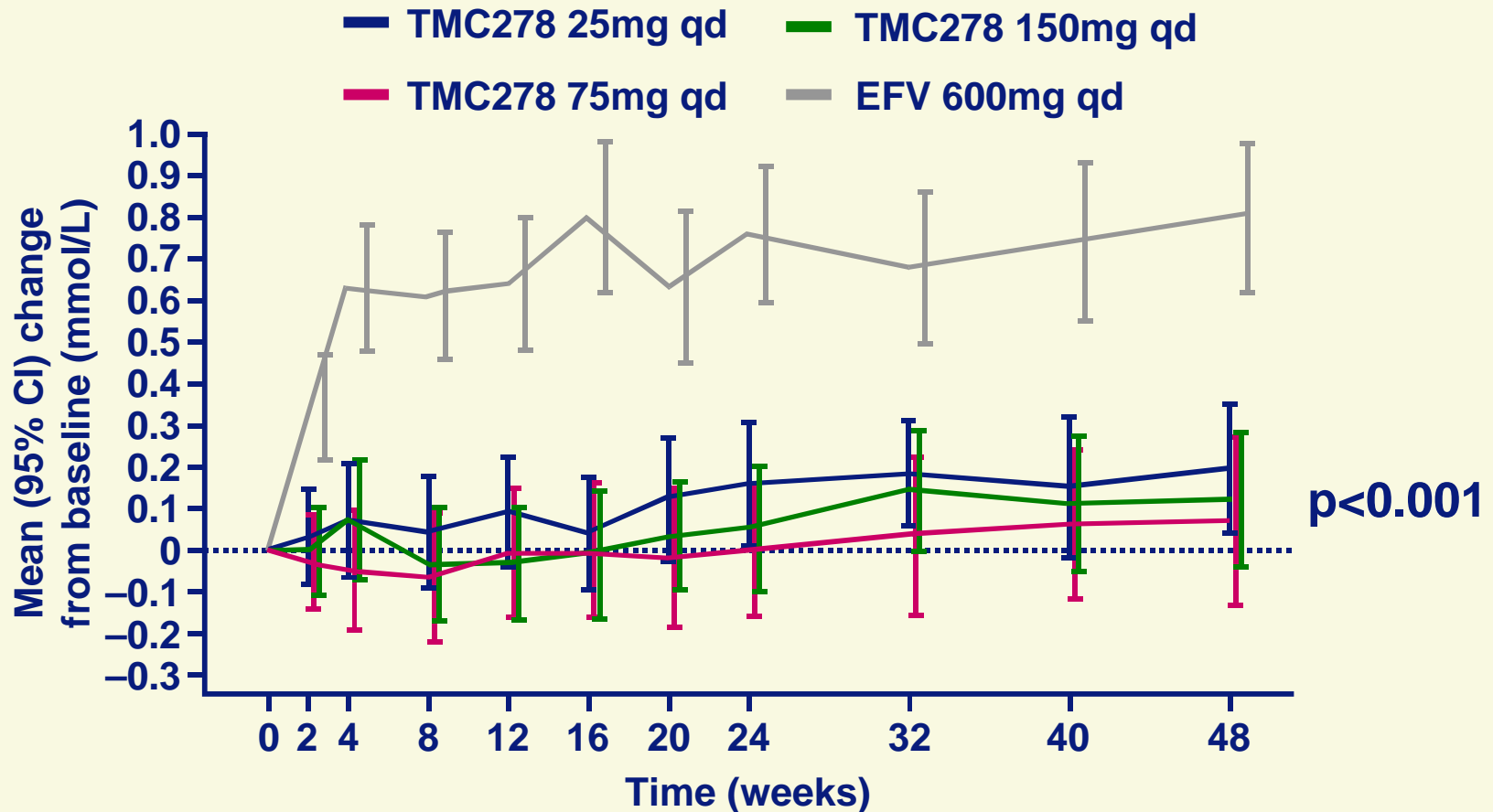
Parameter†	TMC278			Combined TMC278 group	EFV 600mg group
	25mg	75mg	150mg		
TC (mg/dL)	8 (27)	3 (35)	5 (28)	5 (30)**	31 (30)
LDL-C (mg/dL)	3 (24)	1 (28)	-1 (24)	1 (25)**	15 (23)
HDL-C (mg/dL)	5 (8)	6 (9)	5 (10)	5 (9)**	12 (10)
Ratio TC/HDL-C	-0.4 (1.0)	-0.6 (1.0)	-0.4 (0.9)	-0.5 (1.0)	-0.3 (0.9)
TG (mg/dL)	-5 (76)	-19 (76)	-5 (85)	-10 (79)*	18 (66)
Glucose (mg/dL)	2 (14)	1 (11)	2 (12)	1 (12)*	3 (14)
Log (HOMA-IR)	0.7 (0.7)	0 (0.6)	0.2 (0.7)	0.2 (0.7)	0.1 (0.7)

\*p<0.05, \*\*p<0.001 versus EFV (Non-Parametric Wilcoxon rank-sum test; post-hoc analyses)

†Mean change from baseline (standard deviation)

# Mean changes in total cholesterol over time

- There was a clear increase from baseline in TC for the EFV group, but a minimal increase for the TMC278 dose groups

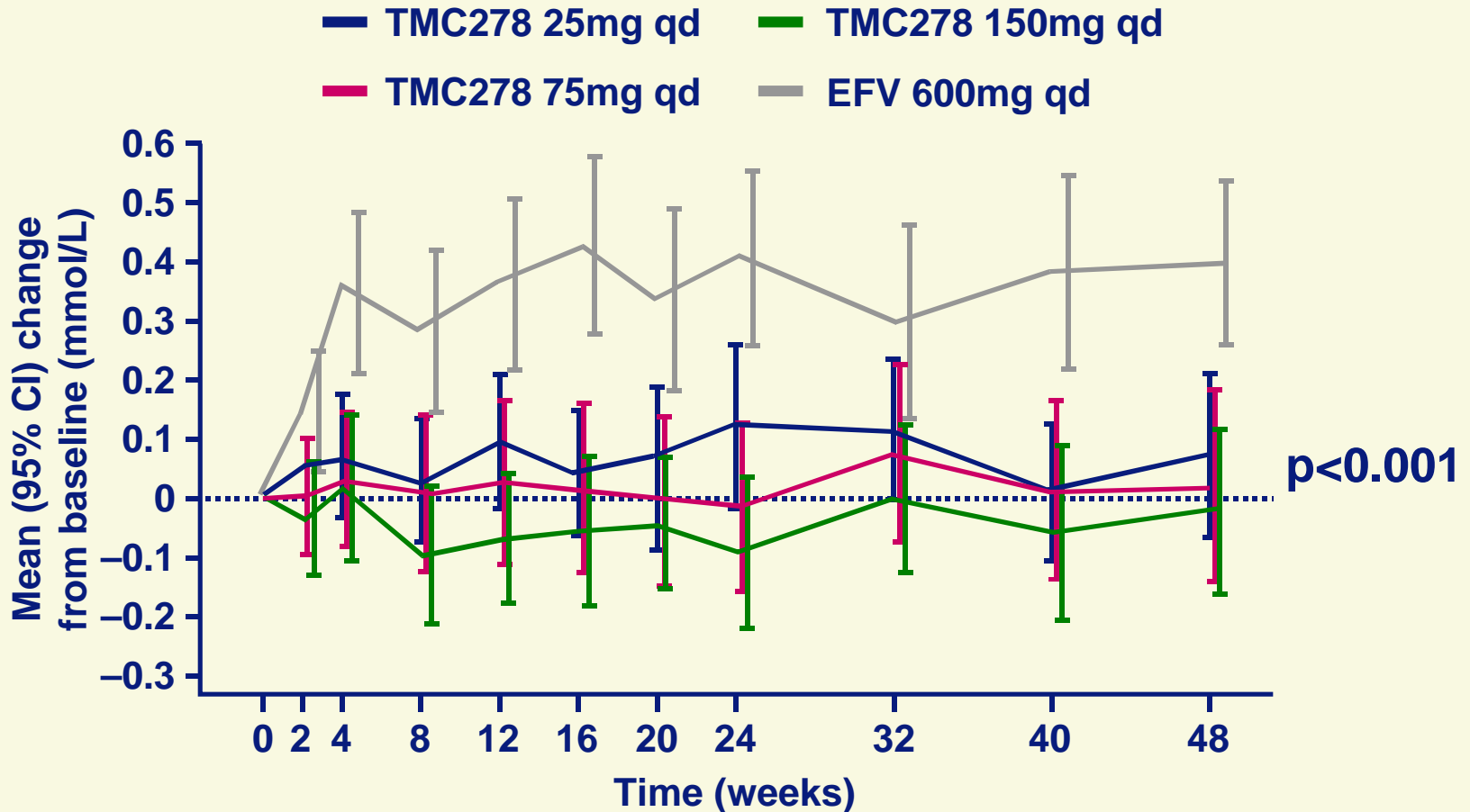


CI = confidence interval;

P values versus EFV (Non-Parametric Wilcoxon rank-sum test; post-hoc analyses)

# Mean changes in LDL-C over time

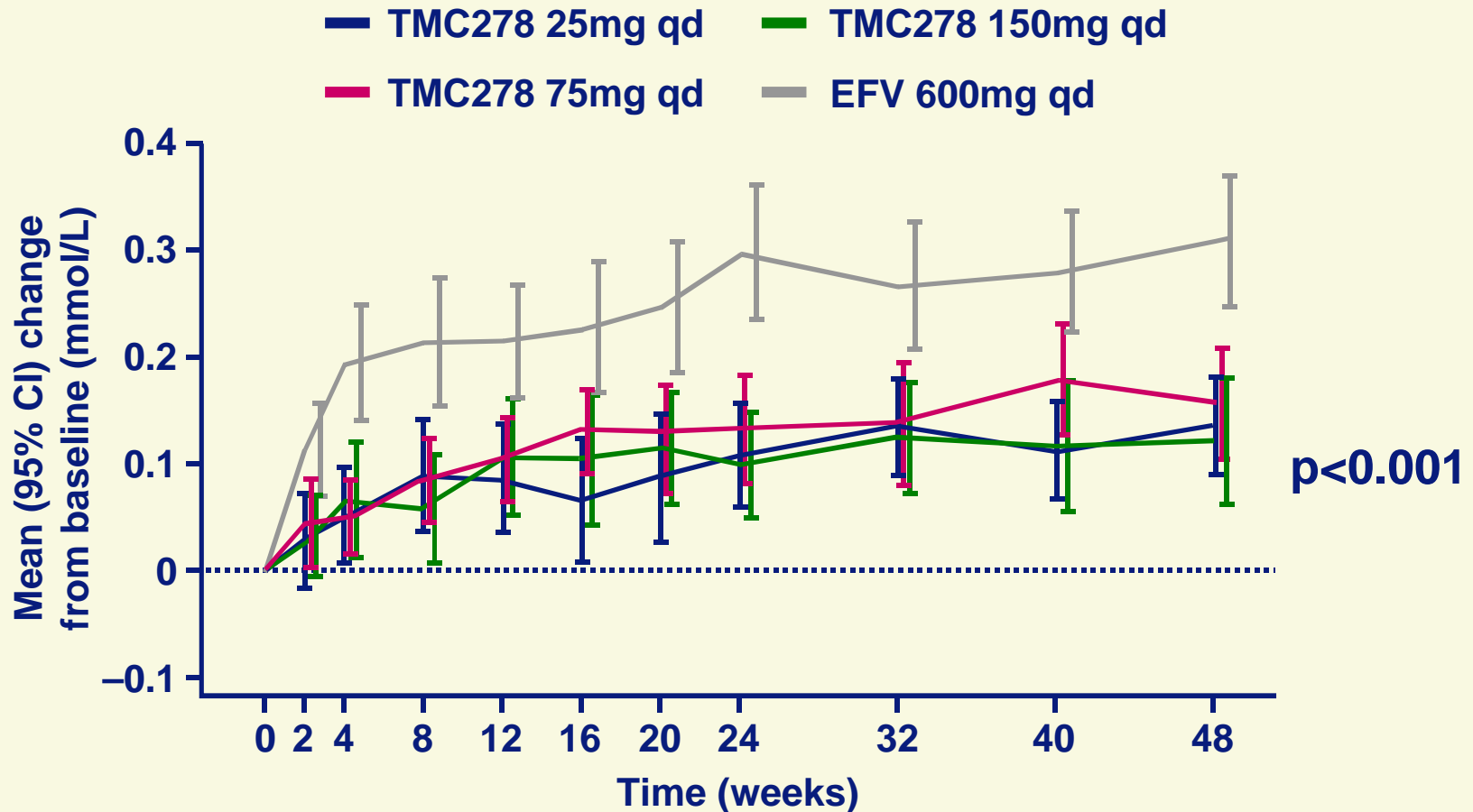
- There was a clear increase from baseline in LDL-C for the EFV group, but not for the TMC278 dose groups



P values versus EFV (Non-Parametric Wilcoxon rank-sum test; post-hoc analyses)

# Mean changes in HDL-C over time

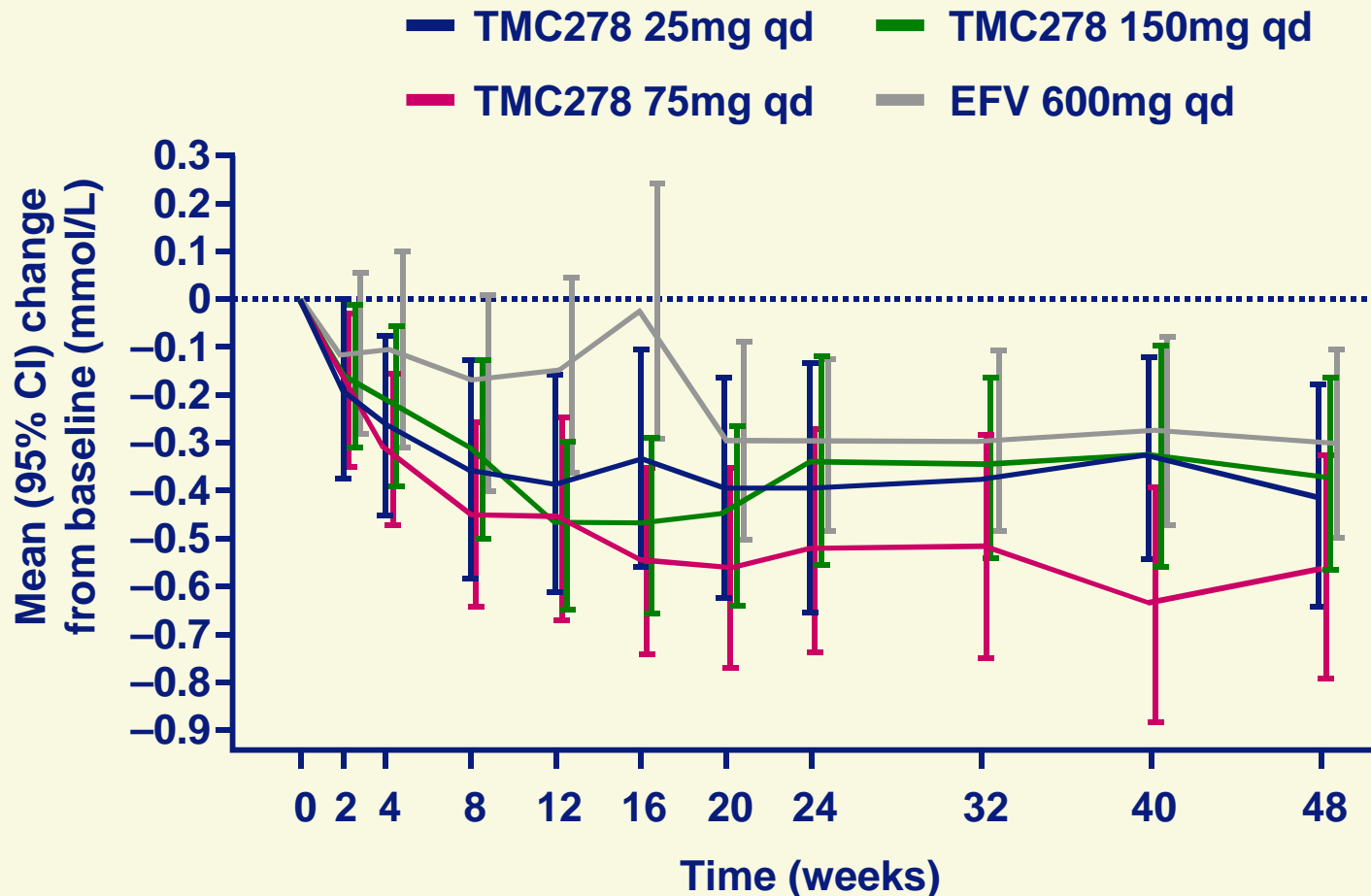
- HDL-C levels increased over time in all groups, but more so in the EFV group than in the TMC278 dose groups



P values versus EFV (Non-Parametric Wilcoxon rank-sum test; post-hoc analyses)

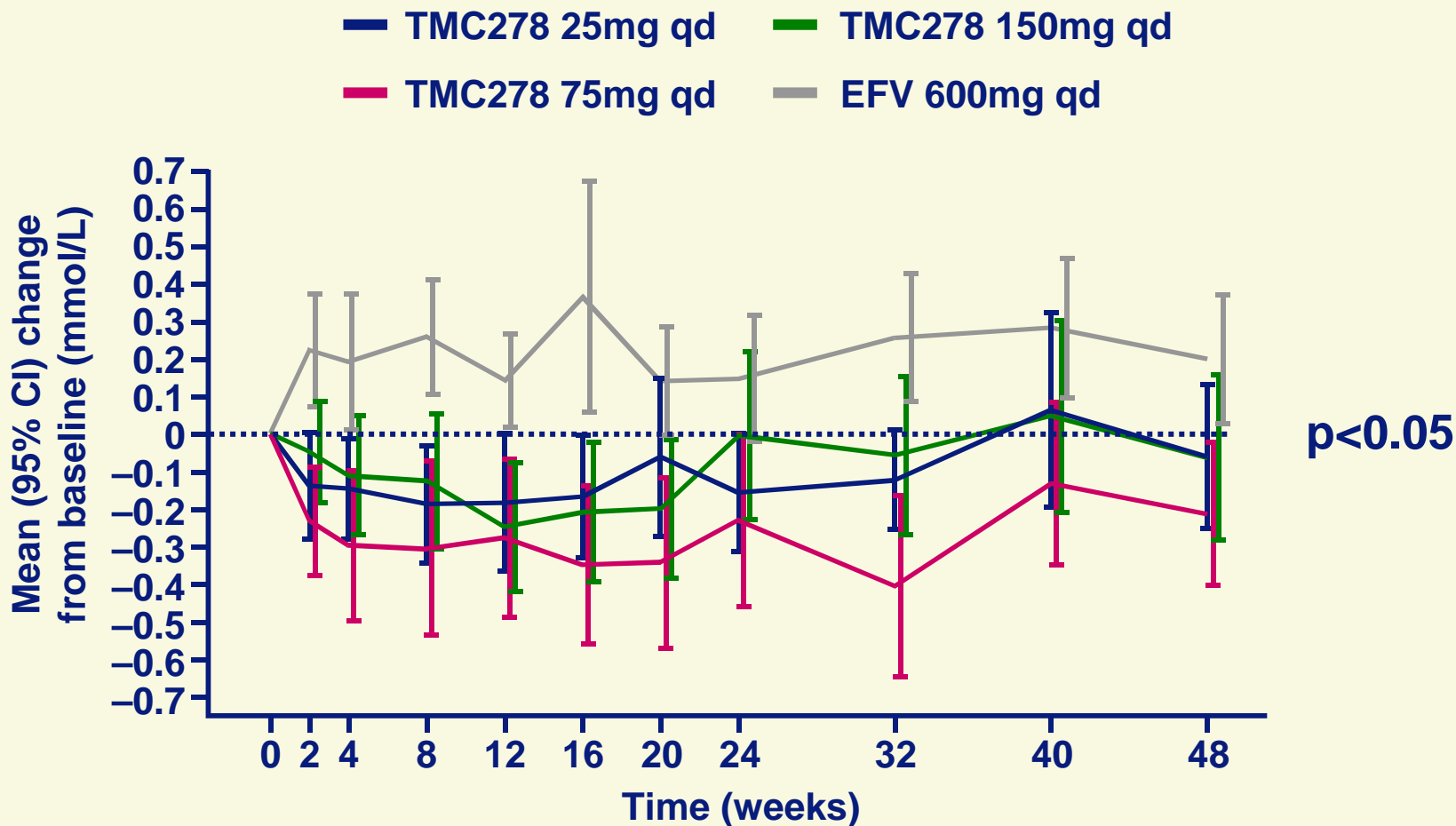
# Mean changes in TC/HDL-C ratio over time

- The TC/HDL-C ratio declined from baseline in all groups, the decline was not significantly different among groups



# Mean changes in triglycerides over time

- There was a small increase from baseline in triglycerides for the EFV group, but not for the TMC278 dose groups



P values versus EFV (Non-Parametric Wilcoxon rank-sum test; post-hoc analyses)

# TMC278-C204 metabolic parameters:

## Conclusions

- TMC278 resulted in minimal changes in lipid profiles at Week 48, and may have a potential benefit *versus* EFV
- No TMC278 dose relationship in metabolic parameters
- Mean changes from baseline in glucose levels and insulin sensitivity were minimal and not clinically relevant for both groups
- Two 96-week Phase III studies are planned to start Q4 2007

# TMC278-C204: acknowledgements

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